MAJOR ARTICLE

Cobicistat Versus Ritonavir as a Pharmacoenhancer of Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-Naive HIV Type 1–Infected Patients: Week 48 Results

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(See the editorial commentary by Cahn and Sued on pages 4–6.)

Background. Cobicistat (COBI) is a pharmacoenhancer with no antiretroviral activity in vitro.

Methods. An international, randomized, double-blind, double-dummy, active-controlled trial was conducted to evaluate the efficacy and safety of COBI versus ritonavir (RTV) as a pharmacoenhancer of atazanavir (ATV) in combination with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) in treatment-naive patients. The primary end point was a human immunodeficiency virus type 1 (HIV-1) RNA load of <50 copies/mL at week 48 by the Food and Drug Administration snapshot algorithm; the noninferiority margin was 12%.

Results. A total of 692 patients were randomly assigned to a treatment arm and received study drug (344 in the COBI group vs 348 in the RTV group). At week 48, virologic success was achieved in 85% of COBI recipients and 87% of RTV recipients (difference, −2.2% [95% confidence interval, −7.4% to 3.0%]); among patients with a baseline HIV-1 RNA load of >100 000 copies/mL, rates were similar (86% vs 86%). Similar percentages of patients in both groups had serious adverse events (10% of COBI recipients vs 7% of RTV recipients) and adverse events leading to discontinuation of treatment with the study drug (7% vs 7%). Median increases in the serum creatinine level were 0.13 and 0.09 mg/dL, respectively, for COBI and RTV recipients.

Conclusions. COBI was noninferior to RTV in combination with ATV plus FTC/TDF at week 48. Both regimens achieved high rates of virologic success. Safety and tolerability profiles of the 2 regimens were comparable. Once-daily COBI is a safe and effective pharmacoenhancer of the protease inhibitor ATV.

Clinical Trials Registration. NCT01108510.

Keywords. cobicistat; pharmacoenhancer; HIV.

The use of a pharmacoenhancer, primarily low-dose (100–400 mg/day) ritonavir (RTV), to boost protease inhibitors (PIs) has had a significant impact on the treatment of human immunodeficiency virus (HIV) infection by improving the pharmacokinetic profiles of the boosted

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drug, resulting in durable efficacy, high barrier to resistance, and a reduced pill burden and dosing frequency [1]. Cobicistat (COBI) is a novel pharmacoenhancer that was developed to boost the plasma levels of elvitegravir (EVG) or PIs. Preclinical studies demonstrated that COBI is more selective than RTV in inhibiting CYP3A; has a low potential for induction, which may lead to fewer or more-predictable drug-drug interactions; and does not have antiretroviral activity in vitro, which eliminates any potential of conferring PI resistance when used as a pharmacoenhancer of a non-PI, such as EVG [2].

In a phase 2 study of treatment-naive patients, COBI was well tolerated and demonstrated similar efficacy to RTV as a pharmacoenhancer for atazanavir (ATV) in combination with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) [3]. ATV was selected as the PI to be boosted by COBI because it is the preferred PI for treatment-naive patients [4, 5]. COBI was also studied as a component of a single-tablet regimen, Stribild (EVG/COBI/FTC/TDF), in 2 large randomized controlled trials that demonstrated its efficacy and safety [6, 7].

In this article, we present results of a phase 3 study in treatment-naive patients that compared COBI to RTV as a pharmacoenhancer for ATV in combination with FTC/TDF.

METHODS

Patients

Study GS-US-216-0114 (clinical trials registration NCT01108510) is an ongoing phase 3 study assessing the efficacy and safety of COBI versus RTV in combination with ATV and FTC/TDF as initial HIV treatment. The study is being conducted internationally and was approved by institutional review boards or ethics committees at all investigative centers. All patients gave written informed consent.

Patients (target enrollment, 700) were HIV type 1 (HIV-1)–infected adults at least 18 years old with a plasma HIV-1 RNA level of ≥ 5000 copies/mL and no prior use of antiretroviral agents. An estimated glomerular filtration rate (eGFR) of at least 70 mL/min and sensitivity to ATV, FTC, and TDF by the infecting strain, determined on the basis of HIV-1 genotyping (GeneSeq assay, Monogram Biosciences, South San Francisco, CA), were required at screening. Additional inclusion criteria included aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤5 times upper limit of normal, a total bilirubin level of ≤1.5 mg/dL or a normal direct bilirubin level, an absolute neutrophil count of ≥1000 cells/mm^3, a platelet count of ≥50 000 platelets/mm^3, a hemoglobin level of ≥8.5 g/dL, and a negative result of a serum pregnancy test (if applicable). Positivity for hepatitis B virus surface antigen or hepatitis C virus antibody was allowed. There was no screening CD4$^+$ T-cell count requirement; patients with new AIDS-defining conditions or serious infections within 30 days of screening were excluded.

Randomization and Blinding

Eligible patients were randomly assigned at a 1:1 ratio to receive either COBI or RTV, each administered once daily. Patients also received placebo tablets matching the alternative treatment; thus, investigators, patients, and study staff were blinded to the treatment group. A computer-generated allocation sequence that used a block size of 4 was created by Bracket (San Francisco, CA), and randomization was stratified by screening HIV-1 RNA level (≤100 000 copies/mL and >100 000 copies/mL). Investigators randomly assigned patients to one of the 2 treatment arms by phone or Internet, using an interactive system (provided and managed by Bracket).

Procedures

Study visits occurred at weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48. Patients were to continue blinded treatment assignments with visits every 12 weeks until week 192. Safety was assessed on the basis of laboratory test results, physical examination findings, and adverse events. Laboratory analyses included hematologic analysis, serum chemistry analysis, and urinalysis (Covance Laboratories, Indianapolis, IN) and HIV-1 RNA load (Amplicor HIV–1 Monitor Test [v1.5]; Roche Diagnostics, Rotkreuz, Switzerland). The HIV-1 genotype (for the genes encoding reverse transcriptase and protease only) was analyzed at screening, using the GeneSeq assay. In patients receiving study drugs who had a confirmed HIV-1 RNA load rebound of ≥400 copies/mL or did not achieve <400 copies/mL by or after week 8, protease and reverse transcriptase genotyping and phenotyping assays were done with PhenoSense GT, PhenoSense Integrase, and GeneSeq Integrase (Monogram Biosciences). Preliminary results by treatment group were reviewed by an independent data monitoring committee (IDMC) when half of the patients completed week 12 of follow-up and when all patients completed weeks 24 and 48 of follow-up.

Statistical Analysis

The primary analysis included all clinical, laboratory, and virologic data available after the last patient had completed the week 48 study visit or prematurely discontinued receipt of the study drug. The primary end point was the proportion of patients with virologic suppression (HIV–1 RNA load, <50 copies/mL) at week 48, in accordance with the US Food and Drug Administration (FDA)–defined snapshot analysis; the intention-to-treat (ITT) population was used to assess the noninferiority of COBI treatment, compared with RTV treatment, using a conventional 95% confidence interval (CI) approach with a prespecified noninferiority margin of 12%. In the FDA snapshot analysis, patients with an HIV-1 RNA load of <50 copies/mL between days 309 and 378 (the week 48 window) were classified as having virologic success. Patients with an HIV-1 RNA load of ≥ 50 copies/mL at the week 48 analysis window or no HIV-1 RNA data in the week 48 analysis

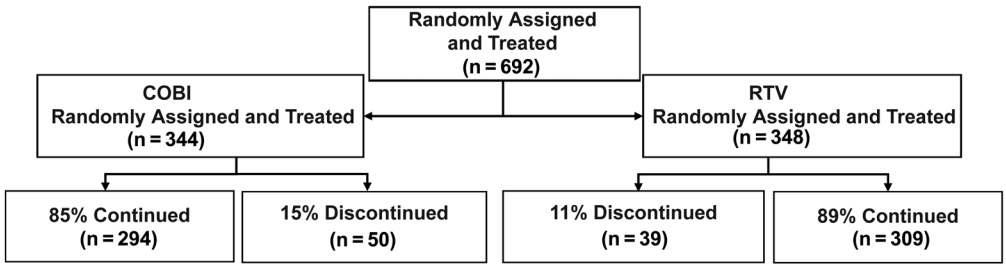
window because of missing data or discontinuation of study drug treatment were considered as not having virologic success. The baseline HIV-1 RNA load stratum (≤100 000 copies/mL or >100 000 copies/mL)–weighted difference in the response rate and its 95% CI were calculated on the basis of a stratum-adjusted Mantel-Haenszel proportion. For each interim analysis performed, an α of 0.001 was spent. Therefore, the significance level for the 2-sided test for virologic response at week 48, according to the FDA snapshot algorithm, for ITT and per-protocol (PP) populations was 0.048, corresponding to a 95.2% CI. A sample size of 700 patients provided at least 95% power to establish noninferiority with respect to the percentage of patients achieving virologic success at week 48, as defined by the FDA snapshot analysis, between the 2 treatment groups. This assumes response rates of 79.5% in both treatment groups [8], a noninferiority margin of 12%, and a significance level of the test at a 1-sided, 0.025 level. Calculations were made using nQuery Advisor, version 6.0 (Statistical Solutions, Saugus, MA).

A per-protocol snapshot analysis was conducted that included all patients who (1) were randomized into the study, (2) received at least 1 dose of study drug, and (3) did not meet any prespecified criteria, such as discontinuation of study drug treatment for reasons other than lack of efficacy with no week 48 HIV-1 RNA load data. Supporting analyses included subgroup analyses (ie, by age, sex, race, baseline HIV–1 RNA level, baseline $CD4^+$ T-cell count, and study drug adherence as assessed by pill counts) to assess treatment differences between specified subgroups. Additional efficacy end points at week 48 were the achievement and maintenance of an HIV-1 RNA load of <50 copies/mL, using the FDA-defined time to loss of virologic response (TLOVR) algorithm [9]; the percentage of patients with an HIV-1 RNA load of <50 copies/mL, using missing-equals-failure and missing-equals-excluded methods; the change from baseline in the HIV-1 RNA load (measured as $\log_{10}$ copies/mL); and the change from baseline in the $CD4^+$ T-cell count.

The safety analysis set included all randomly assigned patients who received at least 1 dose of study drug. All safety data collected on or after the date the study drug was first administered and up to 30 days after the last dose of the study drug (if patients discontinued treatment with the study drug) were summarized descriptively by treatment group. Safety assessments included adverse events, concomitant medication use, laboratory tests (chemistry analysis, hematologic analysis, urinalysis, and urine pregnancy analysis), 12-lead electrocardiograms, height, and weight. Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 14.0. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault method. The Fisher exact and Wilcoxon rank sum tests were used to compare treatment-specific differences in adverse event and continuous laboratory results, respectively (SAS, version 9.2; SAS Institute, Cary, NC).

RESULTS

Screening of patients began in April 2010, and by November 2010, 698 patients had been randomly assigned to receive COBI or RTV. Of these patients, 692 received one of the study medications, with 344 receiving COBI and 348 receiving RTV (Figure 1). Demographic and general baseline characteristics



25	Adverse event	25
11	Lost to follow-up	4
4	Patient noncompliance	3
4	Withdrew consent	2
3	Investigator discretion	1
2	Lack of efficacy	0
1	Pregnancy	3
0	Protocol violation	1
0	Death	0

Figure 1. Patient disposition through week 48 of the study. Abbreviations: COBI, cobicistat; RTV, ritonavir.

Table 1. Baseline Characteristics of Patients

Characteristic	COBI (n = 344)	RTV (n = 348)
Age, y	37 ± 9.8	38 ± 9.6
Women	57 (16.6)	61 (17.5)
Race		
American Indian or Alaska Native	1 (0.3)	2 (0.6)
Asian	44 (12.8)	37 (10.6)
Black or African heritage	65 (18.9)	63 (18.1)
Native Hawaiian or Pacific Islander	1 (0.3)	1 (0.3)
White	198 (57.6)	215 (61.8)
Other	33 (9.6)	27 (7.8)
Unknown	2 (0.6)	3 (0.9)
Hispanic/Latino ethnicity	98 (28.5)	92 (26.4)
Body mass index, kg/m^2[a]	25.2 ± 4.54	25.0 ± 4.70
HBsAg positivity	16 (4.7)	9 (2.6)
HCV antibody positivity	21 (6.1)	16 (4.6)
HIV-1 RNA load		
Log_{10} copies/mL, median	4.78	4.84
>100 000 copies/mL	132 (38.4)	143 (41.1)
CD4$^+$ T-cell count, cells/mm^3	353 ± 170.5	351 ± 175.5
≤200	60 (17.4)	57 (16.4)
201 to ≤350	114 (33.1)	126 (36.2)
351 to ≤500	123 (35.8)	117 (33.6)
>500	47 (13.7)	48 (13.8)

Data are no. (%) of patients or mean value ± SD, unless otherwise indicated.

Abbreviations: COBI, cobicistat; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; RTV, ritonavir.

[a] Calculated as the weight in kilograms divided by the height in meters squared.

Table 2. Virologic Outcome at Week 48 for the Intention-to-Treat Set, Using Food and Drug Administration Snapshot Analysis

Virologic Outcome	COBI (n = 344)	RTV (n = 348)
Virologic success (HIV-1 RNA load of <50 copies/mL)[a]	293 (85.2)	304 (87.4)
	Difference: −2.2% (95% CI: −7.4 to 3.0%) (P = 0.40)	
Virologic failure	20 (5.8)	14 (4.0)
HIV-1 RNA load ≥50 copies/mL	6 (1.7)	7 (2.0)
DC study drug because of lack of efficacy	1 (0.3)	0
DC study drug for other reasons[b]; last available HIV-1 RNA load ≥50 copies/mL	13 (3.8)	7 (2.0)
No virologic data in week 48 window	31 (9.0)	30 (8.6)
DC study drug because of AEs or death	22 (6.4)	23 (6.6)
DC study drug for other reasons[b]; last available HIV-1 RNA load < 50 copies/mL	9 (2.6)	7 (2.0)
Missing data during window but on study drug	0	0

Data are no. (%) of patients.

Abbreviations: AE, adverse event; COBI, cobicistat; DC, discontinued; HIV-1, human immunodeficiency virus type 1; RTV, ritonavir.

[a] Defined as an HIV-1 RNA load of <50 copies/mL between days 309 and 378 (the week 48 window). The difference between the groups and its 95.2% confidence interval were calculated on the basis of baseline HIV-1 RNA load stratum–adjusted Mantel-Haenszel proportion analysis.

[b] Includes investigator's discretion, withdrawal of consent, loss to follow-up, treatment noncompliance, protocol violation, and pregnancy.

were similar between the 2 treatment groups (Table 1). Overall, 39.7% of patients had a baseline HIV-1 RNA load of > 100 000 copies/mL. There was no difference in baseline eGFR between the treatment groups. Rates of discontinuing treatment with the study drug and reasons for discontinuation were similar between treatment groups. The last patient's week 48 visit was completed in November 2011. At interim reviews and week 48, the IDMC recommended that the study continue as planned.

The study met its primary objective of evaluating the noninferiority of COBI versus RTV in combination with ATV and FTC/TDF. In the COBI group, 293 of 344 patients (85.2%) had an HIV-1 RNA load of < 50 copies/mL at week 48, compared with 304 of 348 patients (87.4%) in the RTV group, by the FDA snapshot ITT analysis (difference, −2.2% [95% CI, −7.4% to 3.0%]; Table 2). Other efficacy end points also indicated that virologic responses to COBI and RTV were similar (Supplementary Table 1), including the FDA-defined TLOVR analysis, which showed comparable virologic suppression rates (82.8% [285 of 344] in the COBI group and 85.3% [297 of 348] in the RTV group; difference, −2.6% [95% CI, −8.1% to 2.8%]). The proportion of patients with an HIV-1 RNA load of < 50 copies/mL, determined by missing-equals-failure ITT analysis, was also comparable between the 2 groups (Figure 2).

Responses to COBI were comparable to response to RTV across patient subgroups at week 48 (Supplementary Figure 1), including patients with an HIV-1 RNA load of > 100 000 copies/mL

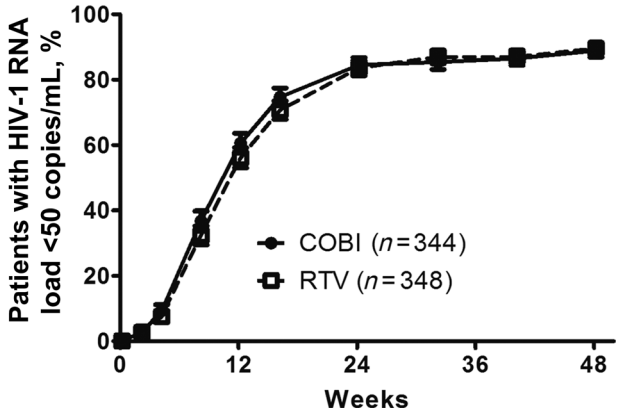


Figure 2. Patients achieving a human immunodeficiency virus type 1 (HIV-1) RNA load of < 50 copies/mL through week 48 of the study, according to missing-equals-failure intention-to-treat analysis. Abbreviations: COBI, cobicistat; RTV, ritonavir.

Table 3. Common Adverse Events (AEs) Occurring in ≥10% of Patients in Either Group

AE	COBI (n = 344)	RTV (n = 348)	*P*
Jaundice	72 (20.9)	54 (15.5)	.076
Scleral icterus	61 (17.7)	64 (18.4)	.84
Nausea	61 (17.7)	57 (16.4)	.69
Diarrhea	53 (15.4)	71 (20.4)	.093
Headache	38 (11.0)	54 (15.5)	.093
Nasopharyngitis	37 (10.8)	53 (15.2)	.09
Hyperbilirubinemia	39 (11.3)	34 (9.8)	.54
URTI	35 (10.2)	28 (8.0)	.36

Data are no. (%) of patients.

Abbreviations: COBI, cobicistat; RTV, ritonavir; URTI, upper respiratory tract infection.

Table 4. Adverse Events (AEs) Leading to Discontinuation of Study Drug in >1 Patient in Either Group

AE	COBI (n = 344)	RTV (n = 348)
Scleral icterus	8 (2.3)	4 (1.1)
Jaundice	9 (2.6)	7 (2.0)
Hyperbilirubinemia	1 (0.3)	2 (0.6)
Rash	1 (0.3)	2 (0.6)
Allergic dermatitis	2 (0.6)	0

Data are no. (%) of patients.

Abbreviations: COBI, cobicistat; RTV, ritonavir.

at baseline (86.4% and 86.0%, respectively). Mean changes in $CD4^+$ T-cell counts at most time points were similar in the COBI and RTV groups (+213 cells/mm^3 and +219 cells/mm^3, respectively, at week 48).

Of the 692 randomly assigned and treated patients, 24 (3.5%) met criteria for resistance testing, with 12 of 344 (3.5%) in the COBI group and 12 of 348 (3.4%) in the RTV group. Of the 10 patients in the COBI group with available data, none developed resistance mutations to PIs or TDF; 2 developed resistance mutations to FTC (M184V). Of the 12 patients in the RTV group, none developed resistance mutations.

Reported adverse events are summarized in Table 3. Most adverse events reported in each group were mild or moderate. No patients died during the study. The numbers of patients who discontinued treatment because of an adverse event were identical in the 2 groups (25 [7.3%] in the COBI group and 25 [7.2%] in the RTV group; Table 4). The most common adverse events, such as hyperbilirubinemia, jaundice, and scleral icterus, were related to an elevated bilirubin level, which occurred in a similar percentage of patients in the COBI and RTV groups (40.7% and 36.2%, respectively); these were also the most common adverse events leading to discontinuation of treatment in both groups (3.5% in the COBI group and 3.2% in the RTV group). The rates of diarrhea and nausea did not differ between the 2 groups.

Renal adverse events leading to treatment discontinuation were reported for 6 patients (1.7%) in the COBI group and 5 patients (1.4%) in the RTV group. In the COBI group, 1 of the 6 patients had baseline serum creatinine level of 0.86 mg/dL and an eGFR of 70.0 mL/min and had treatment discontinued in accordance with the study protocol because of a confirmed eGFR of < 50 mL/min, although the absolute change in serum creatinine level was small (approximately +0.4 mg/dL); the patient's serum creatinine level improved to 0.95 mg/dL after discontinuation of study treatment. The other 5 COBI recipients had laboratory findings consistent with proximal tubulopathy, such as hypophosphatemia, proteinuria, or normoglycemic glycosuria; 4 of these 5 patients had follow-up data available. All 4 patients experienced improvement in their renal laboratory values (serum creatinine, serum phosphate, urine protein, and urine glucose levels) after discontinuing treatment with the study drug. One patient had a complete reversal of the serum creatinine level and all 3 other abnormal findings. The other 3 patients had complete reversal of hypophosphatemia, proteinuria, or glycosuria, while the serum creatinine level improved. One COBI recipient had no follow-up data after developing proximal tubulopathy in the setting of *Enterobacter* sepsis and acute renal failure (serum creatinine level, 5.07 mg/dL; eGFR, 17 mL/min). In the RTV group, 3 of the 5 patients had increases in the serum creatinine level that were not accompanied by features of proximal tubulopathy. In the other 2 patients who had proximal tubulopathy, the serum creatinine level improved, and other markers of proximal tubulopathy completely reversed; 1 patient started a regimen containing RTV. No patient required dialysis. A small increase in the median serum creatinine level between baseline and week 48 was seen in the COBI and RTV groups (+0.13 mg/dL and +0.09 mg/dL, respectively; $P < .001$), and a corresponding decrease in the median eGFR was also observed during this interval (−12.9 mL/min and −9.1 mL/min, respectively; $P < .001$). Most of the change in serum creatinine level in both groups occurred by week 8, with little progression between weeks 8 and 48 (Figure 3).

Because of the safety profile of TDF, bone safety was assessed. Fractures occurred in 2 patients (0.6%) in the COBI group and 4 patients (1.1%) in the RTV group; 1 patient in the RTV group had nontraumatic spinal compression fracture, which was considered old and not acute; all other fractures were trauma related.

As expected with the use of boosted ATV, hyperbilirubinemia was the most common grade 3–4 laboratory abnormality and was more common in the COBI group (65.3%, compared with 56.6% in the RTV group). However, as mentioned above, the rate of treatment discontinuation because of bilirubin-related adverse events was low and similar in both groups. The incidence of grade 3–4 elevation in liver enzyme levels was

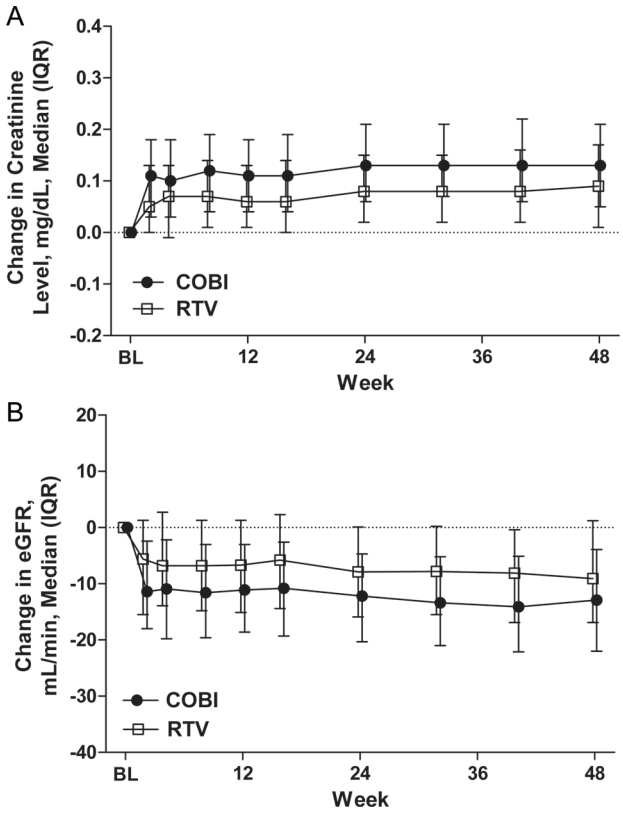


Figure 3. Change in serum creatinine level (*A*) and estimated glomerular filtration rate (eGFR; *B*) through week 48 of the study. Whiskers denote interquartile ranges (IQRs).

similar in the COBI and RTV groups (AST level, 2.9% and 2.0%, respectively; ALT level, 3.2% and 2.0%, respectively). One subject from each group had grade 3–4 elevations in liver enzyme levels (AST or ALT) and hyperbilirubinemia, along with a direct bilirubin level of >1.5 mg/dL, which suggests that the hyperbilirubinemia may not have been associated with ATV. The subject in the COBI group had acute hepatitis C virus infection, and the subject in the RTV group had suspected acute hepatitis B virus infection.

Numerically smaller increases from baseline to week 48 in the COBI group, compared with the RTV group, were observed for fasting total cholesterol level (+5 mg/dL and +9 mg/dL, respectively; $P = .081$) and triglycerides level (+19 mg/dL and +32 mg/dL, respectively; $P = .063$). No other differences were observed between treatment groups in safety-associated laboratory findings, body weight, or electrocardiogram results.

DISCUSSION

In this large, randomized, double-blinded study, COBI demonstrated high efficacy that was comparable and noninferior to that of standard-of-care RTV as a pharmacoenhancer of ATV. The results were consistent across a range of end points, including the primary FDA-defined snapshot analysis, the TLOVR algorithm, and a per-protocol (as-treated) analysis. In addition, the response in the COBI group was comparable to that in the RTV group across all subgroups; virologic success rates in patients with a baseline HIV-1 RNA load of >100 000 copies/mL were high and comparable in the 2 treatment groups. Virologic suppression in this study (85% in the COBI group vs 87% in RTV group) was similar to that seen in other recent randomized clinical trials of boosted PIs plus FTC/TDF at week 48 that reported confirmed virologic response: in the ARTEMIS study, the rate of virologic suppression was 84% in the darunavir (DRV) + RTV group and 78% in the lopinavir (LPV)/RTV group, according to per-protocol analysis [10]; in the CASTLE study, the rate of virologic suppression was 78% in the ATV + RTV group and 76% in the LPV/RTV 76%, according to ITT analysis [11].

In phase 2 trials, COBI rapidly induced a small increase in the serum creatinine level, with a consequent reduction in the eGFR [3, 12, 13]. This phenomenon is due to COBI's inhibition of the tubular secretion of creatinine, with no effect on the actual GFR, as measured by iohexol clearance [13]. RTV has also been shown to inhibit MATE-1, a renal transporter used for tubular secretion of creatinine [14]. Consistent with these findings, a small increase in serum creatinine was seen in both the COBI and RTV group in our study. The changes in serum creatinine level in both groups were observed as early as week 2 and appeared to stabilize by week 8, without further increase through week 48. Some observational studies found that boosted PI regimens used with TDF may be associated with a higher incidence of chronic kidney disease or a greater decrease in the eGFR [15, 16]. However, given the inhibitory effect of RTV on creatinine tubular secretion, studies that use serum creatinine or its derivatives, such as the eGFR, as the primary renal outcome need to be interpreted with caution.

Rates of renal function–associated treatment discontinuation in our study (1.7% in the COBI group vs 1.4% in the RTV group) were consistent with those reported in previous studies. In ACTG5202, 6 of 464 patients (1.3%) receiving ATV boosted by RTV plus FTC/TDF discontinued treatment with or reduced the dose of FTC/TDF because of changes in renal function [17]. Other studies of TDF-containing boosted PI regimens found similar rates, ranging from 0% to 3%, of renal function–associated discontinuation of (or switch from) TDF therapy [18–26]. In our study, a small and similar number of patients discontinued study drug because of proximal tubulopathy (5 COBI recipients and 2 RTV recipients). This is consistent with the safety profile of TDF, which has been associated with proximal tubulopathy (or Fanconi syndrome) [27]. In all patients who developed proximal tubulopathy and had follow-up data, tubular abnormalities (proteinuria, glycosuria, or hypophosphatemia) reversed, and the serum creatinine level improved. The current study will continue in a blinded fashion to further

assess the long-term safety of COBI, including renal safety, using investigator-reported adverse events and renal laboratory parameters (serum creatinine, serum phosphate, urine protein, and urine glucose levels).

The gastrointestinal tolerability of COBI was similar to that of RTV. Gastrointestinal adverse events, such as nausea, vomiting (7.3% vs 4.6%), or diarrhea, were similar between the 2 groups, were mostly of mild severity, and rarely led to discontinuation of study drug treatment (1 COBI recipient discontinued treatment because of vomiting, 1 RTV recipient discontinued because of nausea, and none discontinued because of diarrhea).

Our study does not provide data for HIV-infected patients with lower eGFRs, because an eGFR of at least 70 mL/min was required at study entry. A study to evaluate the use of COBI as a pharmacoenhancer for PI (ATV or DRV) or as a component of the single-tablet regimen EVG/COBI/FTC/TDF in patients with an eGFR of 50–90 mL/min (clinical trials registration NCT01363011) is ongoing.

Notably, the mean baseline $CD4^+$ T-cell count for patients in both treatment arms exceeded 350 cells/mm^3. This high baseline $CD4^+$ T-cell count reflects a trend toward initiation of HIV therapy at earlier stages of disease and is in line with recent HIV treatment guidelines, which recommend antiretroviral therapy for all individuals with HIV infection, regardless of $CD4^+$ T-cell count [4, 5].

The lack of antiretroviral activity of COBI is an advantage over RTV, which may lead to PI resistance if used as a pharmacoenhancer of a non-PI (eg, EVG) [2]. In addition, the physiochemical properties of COBI, such as high intrinsic solubility and dissolution rate, make it amenable to coformulation with ≥1 antiretroviral agent [28]. Currently, COBI is being developed not only as a stand-alone pharmacoenhancer, but also as a component of several fixed-dose combination tablets that contain EVG, ATV, or DRV.

In conclusion, COBI demonstrated high and noninferior efficacy as a pharmacoenhancer of ATV, compared with standard-of-care RTV. The renal safety profile of COBI is similar to that of other TDF-containing, RTV-boosted PI regimens. COBI may become an important alternative to RTV as a pharmacoenhancer.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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